Pages 14379–14395

PART II

FEDERAL REGISTER

VOLUME 29 NUMBER 204

Washington, Saturday, October 17, 1964

Department of Health, Education, and Welfare

Food and Drug Administration

DRUGS

Notice of Proposed Rule Making

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Parts 146, 148i, 148m, 148n, 148p, 148r]

NEOMYCIN SULFATE, TRIACETYLOLEANDOMYCIN, OXYTETRACYCLINE, POLYMYXIN B SULFATE, TYROTHRICIN

Proposed Certification Procedure and Tests and Methods of Assay

The Commissioner of Food and Drugs, in accordance with procedure established in the Federal Food, Drug, and Cosmetic Act (sec. 507, 59 Stat. 463 as amended; 21 U.S.C. 357) and under the authority delegated to him by the Secretary of Health, Education, and Welfare (21 CFR 2.90; 29 F.R. 471), proposes to issue regulations providing for certification and tests and methods of assay for certain antibiotic and antibiotic-containing drugs.

Before enactment of the "Drug Amendments of 1962" these drugs had been cleared for marketing under the safety provisions of the new drug section of the Federal Food, Drug, and Cosmetic Act. The "Drug Amendments of 1962" provided for certification of the drugs under the antibiotic section of the law (sec. 507). It further specified that if the new-drug approvals had not been withdrawn on the day immediately preceding the effective date (April 30, 1963), the initial issuance of regulations providing for certification of the drugs under the antibiotic section of the law (sec. 507) shall not be conditioned upon an affirmative finding of efficacy of the drugs. Accordingly the initial issuance of regulations cannot be and is not conditioned upon an affirmative finding of efficacy of the drugs involved.

The review of efficacy of the drugs covered by this proposal has not been completed. When completed it may indicate, for any of the products, no need for change, a need for modification of the regulation, or a need to revoke the regulation. Any changes that appear to be needed, based upon efficacy considerations, will be published at a later date as proposals.

A proposed regulation for tests and methods of assay and certification of oxytetracycline troches was published in the FEDERAL REGISTER of April 18, 1963 (28 F.R. 3839). Final action on the oxytetracycline troches proposal will be taken concurrently with that on the proposals in this notice and will be conditioned on the statutory requirements as set forth in the preamble of this notice.

All interested persons are hereby invited to submit written views and comments on these proposals, preferably in quintuplicate, within 30 days from the date of the publication of this notice in the FEDERAL REGISTER, addressed to the Hearing Clerk, Department of Health, Education, and Welfare, Room 5440, 330 Independence Avenue SW., Washington, D.C., 20201.

A. It is proposed to amend § 146.1 *Definitions and interpretations applicable to all certifiable antibiotic drugs* as follows by adding to paragraphs (a), (b), and (d) the following new subparagraph, and by adding the following new subdivision to paragraph (c)(2) to read as follows:

§ 146.1 Definitions and interpretations applicable to all certifiable antibiotic drugs.

(a) * * *

(20) Each of the antibiotic substances produced by the triacetylation of oleandomycin, and each of the same substances produced by any other means, is a kind of triacetyloleandomycin.

* * * * *

(b) * * *

(29) The term "triacetyloleandomycin master standard" means a specific lot of triacetyloleandomycin designated by the Commissioner as the standard of comparison in determining the potency of the triacetyloleandomycin working standard.

* * * * *

(c) * * *

(2) * * *

(xxiii) The term "microgram" applied to triacetyloleandomycin means the activity (potency), calculated as the molecular equivalent of the oleandomycin base, contained in 1.2315 micrograms of the triacetyloleandomycin master standard when dried for 3 hours at 60° C. and a pressure of 5 millilliters or less.

* * * * *

(d) * * *

(24) The term "triacetyloleandomycin working standard" means a specific lot of a homogenous preparation of triacetyloleandomycin.

* * * * *

B. It is proposed to amend Parts 148i, 148m, 148n, 148p, and 148r by adding the following new sections:

§ 148i.13 Neomycin sulfate-hydrocortisone acetate suspension for intra-articular use.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-hydrocortisone acetate suspension for intra-articular use contains, in each milliliter, 3.5 milligrams of neomycin and 50 milligrams of hydrocortisone acetate. It contains one or more suitable preservatives, dispersants, and buffers. It is sterile. It passes the toxicity test. Its pH is not less than 5.3 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (iii), (vi), and (vii). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, pyrogens, pH, and identity.

(*b*) The batch for potency, sterility, toxicity, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch:

(*1*) For all tests except sterility: A minimum of eight immediate containers.

(*2*) For sterility testing: 20 immediate containers, collected at regular intervals throughout each filling operation.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*)(*1*), and (*c*) of this paragraph; $12.00 for all immediate containers in the sample submitted in accordance with subparagraph (3)(ii) (*b*)(*2*) of this paragraph; $24.00 for all containers in the samples submitted for any repeat sterility test, if necessary, in accordance with § 141.2(f) of this chapter.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b)(1), except prepare a stock solution of convenient concentration by placing an accurately measured representative portion of the sample into an appropriate-sized volumetric flask and diluting to volume with 0.1*M* potassium phosphate buffer, pH 8.0. Further dilute an aliquot of the stock solution to the proper prescribed reference concentration with 0.1*M* potassium phosphate buffer, pH 8.0. Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 115 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Sterility.* Proceed as directed in § 141.2 of this chapter, using the method described in paragraph (e)(2) of that section, except transfer 0.25 milliliter in lieu of 1.0 milliliter.

(3) *Toxicity.* Proceed as directed in § 141a.4 of this chapter, using 0.5 milliliter of a solution containing 200 micrograms (estimated) of neomycin per milliliter in sterile distilled water.

(4) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.17 Neomycin sulfate-polymyxin B sulfate oral solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate oral solution contains, in each milliliter, 9.1 milligrams of neomycin and 1,000 units of polymyxin B. It contains one or more suitable flavorings, colorings, and preservatives. Its pH is not less than 6.0 and not more than 7.5. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (iv), (vi), (vii), and (ix) of this

chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content, polymyxin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b) (1), except prepare the sample for assay as follows: Remove an accurately measured representative portion and dilute with sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Further dilute with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration. Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Remove an accurately measured representative portion and dilute with 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Further dilute in 10 percent potassium phosphate buffer, pH 6.0, to 10 units of polymyxin (estimated) per milliliter. Proceed as directed in § 148p.1(b) (1) of this chapter, except add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter. Its content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.28 Neomycin sulfate-gramicidin-hydrocortisone acetate-phenylephrine hydrochloride-thonzonium bromide-thonzylamine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-hydrochloride-thonzonium bromide-thonzylamine hydrochloride nasal solution is a solution containing, in each milliliter, 0.66 milligram of neomycin, 0.05 milligram of gramicidin, 0.2 milligram of hydrocortisone acetate, 2.5 milligrams of phenylephrine hydrochloride, 0.5 milligram of thonzonium bromide, 10.0 milligrams of thonzylamine hydrochloride, and one or more suitable buffers, preservatives, and surfactants. Its pH is not less than 4.8 and not more than 6.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a) (1) (i), (iv), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a) (1) (i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assay on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, residue on ignition, melting point, and identity.

(*c*) The batch for neomycin content, gramicidin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In the case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.20(b) (1) (i). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin.* Proceed as directed in § 148i.20(b) (1) (iii). Its content of gramicidin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.31 Neomycin sulfate (commercial grade).

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate (commercial grade) is the sulfate salt of a kind of neomycin or a mixture of two or more such salts. It is so purified and dried that:

(i) Its potency is not less than 400 micrograms of neomycin per milligram on the anhydrous basis.

(ii) It passes the toxicity test.

(iii) Its moisture content is not more than 8.0 percent.

(iv) Its pH in an aqueous solution containing 33 milligrams of neomycin sulfate commercial grade per milliliter is not less than 4.0 and not more than 7.5.

(v) It gives a positive identity test for neomycin sulfate.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3(b) of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, toxicity, moisture, pH, and identity.

(ii) Samples required: 10 packages, each containing approximately 300 milligrams.

(4) *Fees.* $4.00 for each container submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148i.1 (b) (1).

(2) *Toxicity.* Proceed as directed in § 148i.1(b) (4).

(3) *Moisture.* Proceed as directed in § 148i.1(b) (5).

(4) *pH.* Proceed as directed in § 148i.1(b) (6).

(5) *Identity.* Proceed as directed in § 148i.1(b) (7).

§ 148i.30 Neomycin sulfate (commercial grade)-aluminum chlorohydroxide cream deodorant.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate (commercial grade)-aluminum chlorohydroxide cream deodorant is neomycin sulfate (commercial grade) and aluminum chlorohydroxide in a suitable cream base. It contains, in each gram, the following:

(i) 1 milligram of neomycin and 120 milligrams of aluminum chlorohydroxide (anhydrous); or

(ii) 1.75 milligrams of neomycin and either 100 milligrams or 176 milligrams of aluminum chlorohydroxide (anhydrous).

It may also contain one or more suitable emollients, perfumes, colorings, dispersants, solubilizers, buffers, and preservatives. The neomycin sulfate (commercial grade) used conforms to the standards prescribed by § 148i.31(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate (commercial grade) used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The batch for potency.

(ii) Samples required:

(*a*) The neomycin sulfate (commercial grade) used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay; potency.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Weigh accurately about 3 grams into a 15-milliliter centrifuge tube, cap the tube with aluminum foil, and heat over a steam bath until the cream is liquefied. Add an accurately measured volume of from 7 to 9 milliliters of a 10 percent solution of ammonia. Stir thoroughly to allow the heavy precipitate of aluminum hydroxide to form. Blend the contents for at least 3 minutes in a suitable homogenizer. Transfer the homogenized mixture into the centrifuge tube and centrifuge for 20 minutes at 3000 revolutions per minute. Remove 1.0 milliliter of the clear supernatant and evaporate to dryness under a stream of air. Dissolve and dilute the residue with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration of neomycin. The potency is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that the product is represented to contain.

§ 148i.30a Neomycin sulfate (commercial grade)-aluminum chlorohydroxide deodorant lotion; neomycin sulfate (commercial grade)-aluminum chlorohydroxide-aluminum chloride deodorant lotion.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate (commercial grade)-aluminum chlorohydroxide deodorant lotion contains neomycin sulfate (commercial grade) and aluminum chlorohydroxide in a suitable lotion vehicle. It contains, in each milliliter, the following:

(i) 1.75 milligrams of neomycin and 100 milligrams of aluminum chlorohydroxide (anhydrous); or

(ii) 3.5 milligrams of neomycin and either 142 milligrams or 152 milligrams of aluminum chlorohydroxide (anhydrous); or

(iii) 1 milligram of neomycin and 160 milligrams of aluminum chlorohydroxide (anhydrous).

Neomycin sulfate (commercial grade)-aluminum chlorohydroxide-aluminum chloride deodorant lotion contains, in each milliliter, 1.75 milligrams of neomycin, 176 milligrams of aluminum chlorohydroxide (anhydrous), and 10 milligrams of aluminum chloride. The preparations may also contain one or more suitable emollients, perfumes, colorings, dispersants, solubilizers, buffers, and preservatives in an aqueous vehicle. Their pH is not less than 3.5 and not more than 6.5. The neomycin sulfate (commercial grade) used conforms to the standards of § 148i.31(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached on or within the package, adequate directions for lay use.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate (commercial grade) used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(*a*) The neomycin sulfate (commercial grade) used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3)(ii) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Remove a 3.0-milliliter portion with a suitable syringe and transfer to a 15-milliliter centrifuge tube. Add an accurately measured volume of from 7 to 9 milliliters of a 10 percent solution of ammonia. Stir thoroughly to allow the heavy precipitate of aluminum hydroxide to form. Blend the contents for at least 3 minutes in a suitable homogenizer. Transfer the homogenized mixture into the centrifuge tube and centrifuge for 20 minutes at 3000 revolutions per minute. Remove 1.0 milliliter of the clear supernatant and evaporate to dryness under a stream of air. Dissolve and dilute the residue with 0.1*M* potassium phosphate buffer, pH 8.0, to the proper prescribed reference concentration of neomycin. The potency is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of neomycin that the product is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.30b Neomycin sulfate-aluminum chlorohydroxide deodorant lotion.

Neomycin sulfate-aluminum chlorohydroxide deodorant lotion conforms to all requirements and is subject to all procedures prescribed by § 148i.30a for neomycin sulfate (commercial grade)-aluminum chlorohydroxide deodorant lotion, except that:

(a) Each milliliter contains 3.5 milligrams of neomycin and 160 milligrams of aluminum chlorohydroxide (anhydrous).

(b) The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1) (i), (v), (vi), and (vii).

§ 148i.36 Neomycin sulfate-polymyxin B sulfate-tyrothricin-benzocaine troches.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-tyrothricin-benzocaine troches are troches composed of neomycin sulfate, polymyxin B sulfate, tyrothricin, and benzocaine with one or more suitable lubricants, binders, fillers, colorings, and flavorings. Each troche contains 3.5 milligrams of neomycin, 1,000 units of polymyxin B, 1.0 milligram of tyrothricin, and 10 milligrams of benzocaine. The moisture content is not more than 2.0 percent. The neomycin sulfate used conforms to the standards of § 148i.1(a)(1) (i), (iv), (v), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (iv), (v), (vi), (vii), and (ix) of this chapter. The tyrothricin used conforms to the standards prescribed by § 148r.1(a)(1) of this chapter. Each other substance used, if its name

is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, moisture, pH, residue on ignition, and identity.

(*c*) The tyrothricin used in making the batch for potency, moisture, and identity.

(*d*) The batch for neomycin content, polymyxin content, tyrothricin content, and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The tyrothricin used in making the batch: 5 packages, each containing approximately 300 milligrams.

(*d*) The batch: A minimum of 30 troches.

(*e*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $1.25 for each troche in the sample submitted in accordance with subparagraph (3)(ii)(*d*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), (*c*), and and (*e*) of this paragraph.

(b) *Tests and method of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Place a representative of troches in a high-speed glass blender and add sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend until the troches are completely disintegrated. Make proper estimated dilutions with 0.1*M* potassium phosphate buffer, pH 8.0, to the prescribed reference concentration. The content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148p.1(b)(1) of this chapter, except:

(*a*) Prepare the sample for assay as follows: Dissolve a representative number of troches in sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Make proper estimated dilutions with 10 percent potassium phosphate buffer, pH 6.0, to the reference concentration of 10 units of polymyxin per milliliter.

(*b*) Add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter. Also add to each concentration of the polymyxin standard curve a quantity of sucrose to yield the same concentration of sucrose as that present when the sample is diluted to contain 10 units of polymyxin per milliliter.

The content of polymyxin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(iii) *Tyrothricin content.* Proceed as directed in § 148r.1(b)(1) of this chapter, except prepare the sample for assay as follows: Dissolve a representative number of troches in sufficient 95 percent alcohol to give a concentration of convenient concentration. Make proper estimated dilutions with 95 percent alcohol to the prescribed reference concentration. The content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148i.37 Neomycin sulfate-gramicidin-propyl *p*-aminobenzoate chewing troches.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin-propyl *p*-aminobenzoate chewing troches are troches composed of neomycin sulfate, gramicidin, and propyl *p*-aminobenzoate with one or more suitable binders, solvents, fillers, masticatory substances, flavorings, colorings, and preservatives. Each troche contains 3.5 milligrams of neomycin, 0.25 milligram of gramicidin, and 2.0 milligrams of propyl *p*-aminobenzoate. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (v), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, moisture, residue on ignition, melting point, identity, and crystallinity.

(*c*) The batch for neomycin content and gramicidin content.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of 30 troches.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $1.00 for each troche in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay; potency*—(1) *Neomycin content.* Proceed as directed in § 148i.1(b)(1) except prepare the sample for assay as follows: Place a representative number of troches in a high-speed glass blender and add sufficient 0.1*M* potassium phosphate buffer, pH 8.0, to give a stock solution of convenient concentration. Blend until the troches are completely disintegrated. Make proper estimated dilutions with 9.1*M* potassium phosphate buffer, pH 8.0, to the prescribed reference concentration. Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(2) *Gramicidin content.* Proceed as directed in § 148f.1(b)(1) of this chapter, except prepare the sample for assay as follows: Place a representative number of troches in an Erlenmeyer flask and add 50 milliliters of 80 percent ethyl alcohol. Shake until the entire outer coating of the troches has been removed. Filter the solution through a cotton plug. Wash the contents of the flask with several portions of 80 percent ethyl alcohol and pass the washings through the cotton plug filter. Quantitatively transfer the combined filtrate to a 100-milliliter volumetric flask and adjust to volume with 80 percent ethyl alcohol. Make proper estimated dilutions with 95 percent ethyl alcohol to the reference concentration.

Its content of gramicidin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

§ 148i.38 Neomycin sulfate-gramicidin-benzocaine troches; neomycin sulfate-gramicidin-propyl *p*-aminobenzoate troches.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin-benzocaine troches or neomycin sulfate-gramicidin-propyl *p*-aminobenzoate troches are troches composed of neomycin sulfate, gramicidin, and benzocaine or propyl *p*-aminobenzoate, with or without one or more suitable fillers, lubricants, colorings, and flavorings. Each troche contains either:

(i) 2.5 milligrams of neomycin, 0.25 milligram of gramicidin, and 10 milligrams of benzocaine; or

(ii) 3.5 milligrams of neomycin, 0.25 milligram of gramicidin, and 2 milligrams of propyl *p*-aminobenzoate.

The moisture content is not more than 3.0 percent. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (v), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, moisture, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, moisture, residue on ignition, melting point, identity, and crystallinity.

(*c*) The batch for neomycin content, gramicidin content, and moisture.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of 30 troches.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $1.00 for each troche in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.1(b)(1), except prepare the sample for assay as follows: Place a representative number of troches in a high-speed glass blender, add a quantity of 0.1*M* potassium phosphate buffer, pH 8.0, to make a stock solution of convenient concentration and blend until troches are completely disintegrated. Make estimated dilutions to the reference concentration with 0.1*M* potassium phosphate buffer, pH 8.0. The content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148f.1(b)(1) of this chapter, except prepare the sample for assay as follows: Place a representative number of troches in an Erlenmeyer flask and add a quantity of 95 percent ethyl alcohol that will give a stock solution of convenient concentration. Stopper the flask and shake on a mechanical shaker until the troches are completely disintegrated. Make proper estimated dilutions to the reference concentration with 95 percent ethyl alcohol. The content of gramicidin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148i.40 Neomycin sulfate-polymyxin B sulfate-methoxamine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-methoxamine hydrochloride nasal solution is a solution containing, in each milliliter, 3.5 milligrams of neomycin, 5,000 units of polymyxin B, 5 milligrams of methoxamine hydrochloride, and one or more suitable buffers and preservatives. Its pH is not less than 4.2 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1)(i), (iv), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assay on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency toxicity, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content, polymyxin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.7(b)(1). Its content of neomycin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Remove an accurately measured representative portion with a suitable syringe and dilute to a convenient concentration with 10 percent potassium phosphate buffer, pH 6.0. Further dilute to a concentration of 10 units of polymyxin per milliliter with 10 percent potassium phosphate buffer, pH 6.0. Proceed as directed in § 148p.1(b)(1) of this chapter, except:

(*a*) Add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter.

(*b*) If the dosage form contains thimerosal as a preservative, adjust the agar for the seed layer by adding 300 milligrams of thioglycolic acid per liter.

Its content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.41 Neomycin sulfate-polymyxin B sulfate-phenylephrine hydrochloride-thenyldiamine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-polymyxin B sulfate-phenylephrine hydrochloride-thenyldiamine hydrochloride nasal solution is a solution containing, in each milliliter, 0.6 milligram of neomycin, 3,000 units of polymyxin B,

5 milligrams of phenylephrine hydrochloride, 0.5 milligram of thenyldiamine hydrochloride, and one or more suitable buffers and preservatives. Its pH is not less than 4.2 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1)(i), (iv), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*c*) The batch for neomycin content, polymyxin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 6 immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii)(*a*), and (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.7(h)(1).

Its content of neomycin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Polymyxin content.* Remove an accurately measured representative portion with a suitable syringe and dilute to a convenient concentration with 10 percent potassium phosphate buffer, pH 6.0. Further dilute to a concentration of 10 units of polymyxin per milliliter with 10 percent potassium phosphate buffer, pH 6.0. Proceed as directed in § 148p.1(b)(1) of this chapter, except:

(*a*) Add to each concentration of the polymyxin standard curve a quantity of neomycin to yield the same concentration of neomycin as that present when the sample is diluted to contain 10 units of polymyxin per milliliter.

(*b*) If the dosage form contains thimerosal as a preservative, adjust the agar for the seed layer by adding 300 milligrams of thioglycolic acid per liter.

Its content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.42 Neomycin sulfate-gramicidin-phenylephrine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin-phenylephrine hydrochloride nasal solution is a solution containing, in each milliliter, either 0.8 milligram of neomycin; 0.05 milligram of gramicidin, and 2.5 milligrams of phenylephrine hydrochloride, or 0.66 milligram of neomycin, 0.05 milligram of gramicidin, and 5.0 milligrams of phenylephrine hydrochloride. It may also contain one or more suitable preservatives, solvents, surfactants, and buffers. Its pH is not less than 4.5 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). The gramicidin used conforms to the standards prescribed by § 148f.1(a)(1)(i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, residue on ignition, melting point, identity, and crystallinity.

(*c*) The batch for neomycin content, gramicidin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii)(*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 148i.20(b)(1)(i). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148i.20(b)(1)(iii). Its content of gramicidin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148i.43 Neomycin sulfate-gramicidin-thonzylamine hydrochloride-thonzonium bromide-phenylephrine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Neomycin sulfate-gramicidin-thonzylamine hydrochloride-thonzonium bromide-phenylephrine hydrochloride nasal solution is a solution containing, in each milliliter, 0.66 milligram of neomycin, 0.05 milligram of gramicidin, 10.0 milligrams of thonzylamine hydrochloride, 0.05 milligram of thonzonium bromide, 2.5 milligrams of phenylephrine hydrochloride, and one or more suitable preservatives, solvents, surfactants, and buffers. Its pH is not less than 4.5 and not more than 7.0. The neomycin sulfate used conforms to the standards prescribed by § 148i.1(a)(1)(i), (iv), (vi), and (vii). The gramicidin used conforms to the standards of § 148f.1(a)(1)(i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The neomycin sulfate used in making the batch for potency, toxicity, pH, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, residue on ignition, melting point, identity, and crystallinity.

(*c*) The batch for neomycin content, gramicidin content, and pH.

(ii) Samples required:

(*a*) The neomycin sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Neomycin content.* Proceed as directed in § 1481.20(b) (1) (i). Its content of neomycin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of neomycin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 1481.20(b) (1) (iii). Its content of gramicidin is satisfactory if it contains not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148m.2 Triacetyloleandomycin.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin is the triacetyl ester of oleandomycin base or a mixture of two or more such esters. It is a white crystalline powder. It is so purified that:

(i) Its potency is not less than 750 micrograms of triacetyloleandomycin per milligram.

(ii) It passes the toxicity test.

(iii) Its moisture content is not more than 1.0 percent.

(iv) Its pH in an aqueous alcohol solution containing 100 milligrams of triacetyloleandomycin per milliliter is not less than 7.0 and not more than 8.5.

(v) Its residue on ignition is not more than 0.1 percent.

(vi) It gives a positive identity test for oleandomycin.

(vii) Its R_f value by paper chromatograph is approximately 0.85. If more than one spot appears on the paper chromatogram, determine its acetyl value, which is not less than 15.3 percent and not more than 16.0 percent.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3(b) of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on the batch for potency, toxicity, moisture, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(ii) Samples of the batch: 10 packages, each containing approximately equal portions of not less than 500 milligrams.

(4) *Fees.* $5.00 for each container in the sample submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Use any one of the following methods; however, the results obtained from the method in subdivision (iii) shall be conclusive.

(i) *Chemical method*—(*a*) *Reagents and equipment.* (*1*) Methyl orange reagent: Shake 0.5*M* boric acid solution for 12 hours (to insure saturation) with an excess of methyl orange indicator. An alternative method is to heat the mixture to about 50° C. and shake for about an hour. Then allow to cool. Filter the saturated dye solution and wash three times with chloroform. Store the dye solution over chloroform.

(*2*) Acid-alcohol solution: Add 2 milliliters of concentrated sulfuric acid to 98 milliliters of absolute methyl alcohol.

(*3*) Glycerin: Reagent grade.

(*4*) Centrifuge tubes: 40 milliliters, glass-stoppered.

(*b*) *Procedure.* Prepare a standard solution in chloroform containing 50.0 milligrams of oleandomycin base in 200 milliliters. Transfer 10.0 milliliters of the solution to a 100-milliliter volumetric flask and dilute to volume with chloroform. Transfer 2.0, 4.0, 6.0, and 8.0 milliliters of this solution to glass-stoppered centrifuge tubes (40-milliliter size) and dilute to a total volume of 20.0 milliliters each with chloroform. To the 20 milliliters of the solution present in each 40-milliliter size centrifuge tube, add 0.2 milliliter of glacial acetic acid, 0.2 milliliter of glycerin, and 0.4 milliliter of methyl orange reagent. Shake for 5 minutes and centrifuge for 3 minutes. Immediately transfer to another tube a 10.0-milliliter aliquot from the chloroform (lower) layer. Care must be exercised to see that no portion of the dye-glycerin phase is included with the chloroform aliquot. Add 1.0 milliliter of acid-alcohol solution to this chloroform aliquot, mix well, and read the absorbancy at 535 mu using a 1-centimeter cell and a suitable photometer and using chloroform, similarly treated, as a blank. Prepare a standard curve, plotting the absorbance values of the standard solution against the concentration expressed in micrograms of oleandomycin base per aliquot. Accurately weigh the sample to be tested to give 50 milligrams (estimated) of oleandomycin base, dissolve in chloroform, and make to 200 milliliters with chloroform. Transfer 10.0 milliliters to a 100-milliliter volumetric flask and make to volume with chloroform. Transfer 5.0 milliliters to a glass-stoppered centrifuge tube and proceed as above. Determine the potency of the sample from the standard curve.

(ii) *Plate bioassay.* Proceed as directed in § 148m.1(b) (1), except:

(*a*) Add 2.0 milliliters of polysorbate 80 to each 100 milliliters of the agar used for the base and seed layers.

(*b*) In lieu of the directions in § 148m.1(b) (1) (iii), dissolve a suitable weighed quantity of the triacetyloleandomycin working standard in sufficient 80 percent isopropyl alcohol-water solution to give a concentration of 1,000 micrograms of triacetyloleandomycin per milliliter. Use the solution the day that it is prepared.

(*c*) In lieu of the directions in § 148m.1(b) (1) (iv), dissolve the sample in sufficient 80 percent isopropyl alcohol-water solution to give a convenient stock solution. Further dilute in 0.2*M* potassium phosphate buffer, pH 10.5, to give a final concentration of 15 micrograms of triacetyloleandomycin per milliliter (estimated).

(*d*) In lieu of the directions in § 148m.1(b) (1) (vi), use the agar described in subdivision (*a*) of this subdivision for both layers. Use the plates as soon after seeding as practical. If they are not to be used immediately after seeding, refrigerate the inoculated plates until ready for use.

(*e*) In lieu of the directions for preparing the standard curve in § 148m.1 (b) (1) (vii), prepare the standard curve by diluting the stock triacetyloleandomycin standard solution in 0.2*M* potassium phosphate buffer, pH 10.5, to give concentrations of 9.6, 12.0, 15.0, 18.8, and 23.4 micrograms of triacetyloleandomycin per milliliter. The 15.0 micrograms per milliliter concentration is the reference concentration.

(*f*) In lieu of the directions in § 148m.1(b) (1) (viii), incubate the plates at 37° C. overnight. The concentration of the sample and standard being tested is 15.0 micrograms of triacetyloleandomycin per milliliter.

(iii) *Turbidimetric bioassay*—(*a*) *Culture media.* Use ingredients that conform to the standards prescribed by the U.S.P. or N.F., if any.

(*1*) Make nutrient agar for carrying the test organism as follows:

Peptone	6.0 gm.
Pancreatic digest of casein	4.0 gm.
Yeast extract	1.5 gm.
Beef extract	1.5 gm.
Dextrose	1.0 gm.
Agar	15.0 gm.
Distilled water, q.s.	1,000.0 ml.

pH 6.5–6.6 after sterilization.

(*2*) Make nutrient broth for preparing an inoculum of the test organism as follows:

Peptone	5.0 gm.
Yeast extract	1.5 gm.
Beef extract	1.5 gm.
Sodium chloride	3.5 gm.
Dextrose	1.0 gm.
Dipotassium phosphate	3.68 gm.
Potassium phosphate	1.32 gm.
Distilled water, q.s.	1,000.0 ml.

pH 7.0 after sterilization.

In lieu of preparing the media from the individual ingredients specified in this subdivision, they may be made from a dehydrated mixture which, when reconstituted with distilled water, has the same composition as such media. Minor modifications of the individual ingredients specified in this subdivision are permissible, if the resulting media possess growth-promoting properties at least equal to the media described.

(b) *Preparation of the inoculated broth.* The test organism in *Klebsiella pneumoniae* (A.T.C.C. 10031), noncapsulated, which is maintained on slants of nutrient agar prepared as described in subdivision (a) (1) of this subdivision. Transfer stock culture of the test organism every week to fresh nutrient agar slants and incubate overnight at 37° C. Suspend the growth from a freshly incubated slant in sterilized U.S.P. saline T.S., and inoculate a large nutrient agar surface such as that provided by a Roux bottle containing 300 milliliters of the nutrient agar. Spread the suspension of organism evenly over the entire nutrient agar surface and incubate overnight at 37° C. Harvest the growth from the surface, using 50 milliliters of sterilized U.S.P. saline T.S. per Roux bottle. Adjust the volume of the suspension so that a 1 + 24 dilution will give 25 percent light transmission when measured with a suitable photoelectric colorimeter having a 580 mμ filter and a 13-millimeter test tube as an absorption cell. The resulting suspension may be used for 1 week when stored under refrigeration. Prepare the daily inoculated broth by adding 0.2 milliliter of the adjusted suspension to each 100 milliliters of nutrient broth prepared as described in subdivision (a) (2) of this subdivision.

(c) *Working standard.* Prepare the daily standard curve by diluting the stock triacetyloleandomycin working standard solution prepared as described in subdivision (ii) (b) of this subparagraph with 1 percent potassium phosphate buffer, pH 6.0, to the following final concentrations: 15.0, 19.5, 25.0, 32.0, and 41.2 micrograms of triacetyloleandomycin per milliliter. The 25.0 micrograms per milliliter concentration is the reference concentration. Add 1 milliliter of each final concentration to each of three tubes having an outside dimension of 16 millimeters by 125 millimeters.

(d) *Preparation of sample.* Dissolve the sample under test with an 80 percent isopropyl alcohol-water mixture to prepare a convenient stock solution. Further dilute the stock solution in 1 percent potassium phosphate buffer, pH 6.0, to the reference concentration of 25 micrograms of triacetyloleandomycin per milliliter (estimated). Add 1 milliliter of the sample reference concentration solution to each of three tubes having an outside dimension of 16 millimeters by 125 millimeters.

(e) *Procedure.* Add 9 milliliters of the inoculated broth prepared as described in subdivision (b) of this subdivision to each of the tubes containing the sample and standard solutions, and immediately incubate in a 37° C. water bath for 3–4 hours. After incubation, remove all tubes and add 0.5 milliliter of 12 percent formaldehyde to each tube. Using a suitable photoelectric colorimeter at the wavelength of 530 mμ set the instrument at zero absorption with clear, uninoculated broth prepared as described in subdivision (a) (2) of this subdivision. Determine the absorption value for each sample and standard tube.

(f) *Estimation of potency.* Plot the average absorption values for each final concentration of the standard on semilogarithmic paper with absorption on the arithmetic scale and concentrations on the logarithmic scale. Construct the straight line of best fit through the points, either by inspection or by means of the following equations:

$$L=\frac{3a+2b+c-e}{5},$$

$$H=\frac{3e+2d+c-a}{5},$$

where:

L = Calculated absorption value for the lowest concentration of the standard curve;

H = Calculated absorption value for the highest concentration of the standard curve;

a, b, c, d, e = Average absorption value for the 15.0, 19.5, 25.0, 32.0, and 41.2 micrograms per milliliter concentrations of the standard curve, respectively.

Plot values obtained for L and H and connect with a straight line. Average the absorption values for the sample and determine the average concentration of the sample solutions from the standard curve. Multiply the concentration by the appropriate dilution factor to determine the triacetyloleandomycin content of the sample.

(2) *Toxicity.* Proceed as directed in § 141d.305(b) of this chapter, except administer a test dose of 0.5 milliliter of a suspension containing 200 milligrams of triacetyloleandomycin per milliliter in U.S.P. saline T.S.

(3) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(4) *pH.* Proceed as directed in § 141a.5(b) of this chapter using a saturated solution prepared by adding 100 milligrams of triacetyloleandomycin per milliliter of water-ethyl alcohol (1:1) diluent.

(5) *Residue on ignition.* Proceed as directed in § 141e.401(g) of this chapter.

(6) *Identity.* Dissolve about 10 milligrams in 5 milliliters of hydrochloric acid and heat the solution in a boiling water bath; a greenish yellow color is produced.

(7) *R_f value.*—(i) *Apparatus and reagents* (a) Chromatographic chamber (cylinder glass-stoppered museum jar 11.5 inches x 3.5 inches).

(b) Chromatographic paper (8 inches x 8 inches Whatman No. 1).

(c) 0.1*N* hydrochloric acid.

(d) Resolving solvent: Butyl acetate, benzene, nitromethane, pyridine (5:5:5:1 by volume).

(e) Spray reagent: 15 grams antimony trichloride per 100 milliliters of chloroform.

(ii) *Procedure.* Dissolve the sample in chloroform to give a solution containing 10 milligrams to 20 milligrams of oleandomycin base equivalent per milliliter. Prepare a sheet of chromatographic paper by drawing a line of origin parallel to and 1 inch from the edge of the paper. Wet the paper thoroughly with the 0.1*N* hydrochloric acid and blot it firmly between sheets of absorbent paper. Starting 2 inches in from the edge and at 1-inch intervals, apply 3 microliters to 5 microliters of the sample solutions to the starting line. Allow a few minutes for the paper to dry partially. While the paper is still damp, form a cylinder by bringing the outer edges together, allowing about 1-inch overlap, and secure with a paper clip. Stand the paper in the chromatographic chamber, which has been filled to a depth of ½ inch with the resolving solvent. After the solvent front rises to a height of 4 inches to 5 inches above the origin, remove the paper from the tank and hang it up to air dry. Spray the dried paper with the antimony trichloride reagent. Hang the paper in a 100°C. oven for 3 minutes. A purple spot becomes visible for triacetyloleandomycin at an R_f value of about 0.85. The approximate R_f values for diacetyloleandomycin, monoacetyloleandomycin, and oleandomycin are, respectively, 0.72, 0.27, and 0.13.

(8) *Acetyl determination*—(i) *Apparatus and reagents.* (a) One 3-necked Pyrex flask of approximately 45 milliliters capacity, pear-shaped with T-joints, agar inlet tube, glass-stoppered funnel, glass condenser, and bubble counter.

(b) 50-milliliter Pyrex Erlenmeyer flask.

(c) 10-milliliter buret, calibrated to 0.02 milliliter.

(d) Anhydrous methyl alcohol, reagent grade.

(e) 2*N* sodium hydroxide solution.

(f) Sulfuric acid solution prepared by adding 100 milliliters of concentrated H_2SO_4 to 200 milliliters of water.

(g) 1*N* barium chloride solution.

(h) Phenolphthalein solution (1 percent in ethyl alcohol).

(i) Water-pumped nitrogen.

(j) NaOH solution, 0.015*N*.

(ii) *Procedure.* Weigh accurately (to 0.01 milligram) approximately 30 milligrams of the sample into the three-necked acetyl flask. Add 2.0 milliliters of methyl alcohol to dissolve the sample, then add slowly with gentle swirling, 1.0 milliliter of NaOH solution. Connect the gas inlet tube with bubble counter attached, and adjust nitrogen flow to about two bubbles a second. Put glass-stoppered funnel in centerneck of acetyl flask, and put about 5 milliliters of H_2O in the funnel. Add a boiling chip to the solution and attach condenser in the refluxing position with water cooling. Adjust burner flame under acetyl flask to reflux solution gently. Reflux for 30 minutes. Cool assembly slightly, then rinse down condenser (still in reflux position) with a few milliliters of H_2O. Reassemble condenser to the distillation position and add water through the funnel to make a total of approximately 5 milliliters of H_2O added to acetyl flask.

Adjust burner flame so that about 5 milliliters of H_2O and methyl alcohol is distilled over in approximately 10 minutes. Discard this distillate. Cool acetyl flask slightly. Acidify solution in flask by adding 1 milliliter of the sulfuric acid solution through the funnel. Adjust burner flame and distill over approximately 20 milliliters of distillate into an Erlenmeyer flask in about 20 minutes, adding water through the funnel as necessary. It is important to keep the liquid volume in the acetyl flask around 2 milliliters to 3 milliliters in order to obtain a quantitative recovery of the acetic acid. Collect a second fraction of distillate, about 10 milliliters in volume. As the second fraction is distilling, process the first fraction. Heat the first fraction and boil gently about 20 seconds. Add a few drops of $BaCl_2$ solution to check if any sulfate was distilled over. If the sulfate is present, discard and repeat the whole determination. If the sulfate is absent, immediately titrate the solution with the 0.015*N* NaOH solution to a faint-pink endpoint, using one drop of phenolphthalein solution as the indicator. Repeat the above procedure with the second fraction. If the second fraction requires less than 0.10 milliliter of the 0.015*N* NaOH solution and all the acetic acid has been distilled over, the determination is completed. If greater than this, collect a third fraction of approximately 10 milliliters and titrate this as before. Total volumes of NaOH used and calculate results as follows:

$$\frac{\text{Milliliters of NaOH} \times N\text{NaOH} \times 0.043 \times 100}{\text{Weight sample in grams}} = \text{Percent acetyl.}$$

(9) *Crystallinity.* Proceed as directed in § 141a.5(c) of this chapter.

§ 148m.4 Triacetyloleandomycin capsules; triacetyloleandomycin-_____ capsules (the blank being filled in with the established names of the other active ingredients present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin capsules are capsules composed of triacetyloleandomycin and one or more suitable buffers, diluents, binders, lubricants, and colorings. Each capsule contains 125 milligrams or 250 milligrams of triacetyloleandomycin. The following other drugs may be combined with triacetyloleandomycin, in the indicated amounts, per capsule: 121 milligrams _____ of triacetyloleandomycin, 120 milligrams of acetophenetidin, 30 milligrams of caffeine, and 150 milligrams of buclizine hydrochloride.

The moisture content is not more than 5.0 percent. The triacetyloleandomycin used conforms to the standards prescribed by § 148m.2(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Request for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The triacetyloleandomycin used in making the batch for potency, toxicity, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency and moisture.

(ii) Simples required:

(*a*) Triacetyloleandomycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch: A minimum of 30 capsules.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each capsule in the sample submitted in accordance with subparagraph (3)(ii)(*b*) of this paragraph; $4.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*a*) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency.* Proceed as directed in § 148m.2(b)(1)(ii) or (iii), except prepare the sample as follows: Place a representative number of capsules in a glass blending jar and add 500 milliliters of 80 percent isopropyl alcohol. Blend for 3 minutes with a high-speed blender; remove an aliquot and make the proper estimated dilutions to the prescribed reference concentration in 0.2*M* potassium phosphate buffer, pH 10.5, if the plate assay method is used, or in 1 percent potassium phosphate buffer, pH 6.0, if the turbidimetric assay is used. Its triacetyloleandomycin content is satisfactory if it contains not less than 90 percent nor more than 120 percent of the number of milligrams of triacetyloleandomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148m.5 Triacetyloleandomycin - sulfadiazine - sulfamerazine - sulfamethazine tablets.

(a) *Requirements for certification—*(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin-sulfadiazine-sulfamerazine-sulfamethazine tablets are tablets composed of triacetyloleandomycin, sulfadiazine, sulfamerazine, and sulfamethazine, with one or more suitable buffers, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains 75 milligrams of triacetyloleandomycin, 111 milligrams of sulfadiazine, 111 milligrams of sulfamerazine, and 111 milligrams of sulfamethazine. The moisture content is not more than 5 percent. The tablets shall disintegrate within 1 hour. The triacetyloleandomycin used conforms to the standards prescribed by § 148m.2(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The triacetyloleandomycin used in making the batch for potency, toxicity, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) Triacetyloleandomycin used in making the batch: 10 packages each containing approximately 500 milligrams.

(*b*) The batch:

(*1*) For all tests except disintegration time: A minimum of 30 tablets.

(*2*) For disintegration time: Six tablets.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each tablet in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*1*) of this paragraph; $3.00 for all tablets in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*2*) of this paragraph; $4.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*a*) of this paragraph.

(b) *Tests and methods of assay—*(1) *Potency.* Proceed as directed in § 148m.2(b)(1)(ii) or (iii), except prepare the sample as follows: Place a representative number of tablets in a glass blending jar and add 500 milliliters of 80 percent isopropyl alcohol. Blend for 3 minutes with a high-speed blender; remove an aliquot and make the proper estimated dilutions to the prescribed reference concentration in 0.2*M* potassium phosphate buffer, pH 10.5, if the plate assay is used, or in 1 percent potassium phosphate buffer, pH 6.0, if the turbidimetric assay is used. Its triacetyloleandomycin content is satisfactory if it contains not less than 90 percent nor more than 120 percent of the number of milligrams of triacetyloleandomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 148m.6 Triacetyloleandomycin-phenylpropanolamine hydrochloride-pheniramine maleate-pyrilamine maleate-calcium acetylsalicylate carbamide tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin-phenylpropanolamine hydrochloride - pheniramine maleate - pyrilamine maleate-calcium acetylsalicylate carbamide tablets are tablets composed of triacetyloleandomycin, phenylpropanolamine hydrochloride, pheniramine maleate, pyrilamine maleate, and calcium acetylsalicylate carbamide, with one or more suitable buffers, diluents, binders, lubricants, colorings, and flavorings. Each tablet contains 125 milligrams of triacetyloleandomycin, 12.5 milligrams of phenylpropanolamine hydrochloride, 6.25 milligrams of pheniramine maleate, 6.25 milligrams of pyrilamine maleate, and 382 milligrams of calcium acetylsalicylate carbamide. The moisture content is not more than 5 percent. The tablets shall disintegrate within 1 hour. The triacetyloleandomycin used conforms to the standards prescribed by § 148m.2(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The triacetyloleandomycin used in making the batch for potency, toxicity, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency, moisture, and disintegration time.

(ii) Samples required:

(*a*) Triacetyloleandomycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*b*) The batch:

(*1*) For all tests except disintegration time: A minimum of 30 tablets.

(*2*) For disintegration time: Six tablets.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each tablet in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*1*) of this paragraph; $3.00 for all tablets in the sample submitted in accordance with subparagraph (3)(ii)(*b*)(*2*) of this paragraph; $4.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $5.00 for each immediate container submitted in accordance with subparagraph (3)(ii)(*a*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148m.2(b)(1)(ii) or (iii), except prepare the sample as follows: Place a representative number of tablets in a glass blending jar and add 500 milliliters of 80 percent isopropyl alcohol. Blend for 3 minutes with a high-speed blender; remove an aliquot and make the proper estimated dilutions to the prescribed reference concentration in 0.2*M* potassium phosphate buffer, pH 10.5, if the plate assay is used, or in 1 percent potassium phosphate buffer, pH 6.0, if the turbidimetric assay is used. Its triacetyloleandomycin content is satisfactory if it contains not less than 90 percent nor more than 120 percent of the number of milligrams of triacetyloleandomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *Disintegration time.* Proceed as directed in § 141a.9(c) of this chapter.

§ 148m.7 Triacetyloleandomycin oral suspension; triacetyloleandomycin-_____ oral suspension (the blank being filled in with the established names of the other active ingredients present in accordance with paragraph (a)(1) of this section).

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin oral suspension is triacetyloleandomycin and one or more suitable buffers, dispersants, flavorings, colorings, and preservatives, suspended in a suitable and harmless vehicle. Each milliliter contains 25 milligrams of triacetyloleandomycin. The following other drugs may be combined with triacetyloleandomycin oral suspension in the indicated amounts per milliliter:

(i) 33 milligrams of sulfadiazine, 33 milligrams of sulfamerazine, and 33 milligrams of sulfamethazine; or

(ii) 2.5 milligrams of phenylpropanolamine hydrochloride, 1.25 milligrams of pheniramine maleate, 1.25 milligrams of pyrilamine maleate, 30 milligrams of acetaminophen.

Its pH is not less than 5.0 and not more than 8.0. The triacetyloleandomycin used conforms to the standards prescribed by § 148m.2(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The triacetyloleandomycin used in making the batch for potency, toxicity, moisture, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency and pH.

(iii) Samples required:

(*a*) Triacetyloleandomycin used in making the batch: 10 packages each containing approximately 500 milligrams.

(*b*) The batch: A minimum of five immediate containers.

(*c*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container in the samples submitted in accordance with subparagraph (3)(ii)(*b*) and (*c*) of this paragraph; $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*a*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceeds as directed in § 148m.2(b)(1)(ii) or (iii), except prepare the sample as follows: Transfer an appropriate sample (usually from 1.0 milliliter to 5.0 milliliters) to a 100-milliliter volumetric flask and dilute to mark with 80 percent isopropyl alcohol-water solution. Further dilute an aliquot of this solution to the prescribed reference concentration in 0.2*M* potassium phosphate buffer, pH 10.5, if the plate assay is used, or in 1 percent potassium phosphate buffer, pH 6.0, if the turbidimetric assay is used. Its triacetyloleandomycin content is satisfactory if it contains not less than 90 percent nor more than 120 percent of the number of milligrams of triacetyloleandomycin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148m.8 Triacetyloleandomycin for oral suspension.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Triacetyloleandomycin for oral suspension is triacetyloleandomycin with suitable buffers, dispersants, preservatives, colorings, and flavorings. When the suspension is prepared as directed in its labeling, each milliliter contains 25 milligrams of triacetyloleandomycin, except if it is for pediatric use each milliliter contains 100 milligrams of triacetyloleandomycin. Its moisture content is not more than 2 percent. The pH of the suspension, when prepared as directed in its labeling, is not less than 5.0 and not more than 7.0. The triacetyloleandomycin used conforms to the standards prescribed by § 148m.2(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The triacetyloleandomycin used in making the batch for potency, toxicity, moisture, pH, residue on ignition, identity, R_f value, acetyl value (only if more than one spot is present in the determination of R_f value), and crystallinity.

(*b*) The batch for potency, moisture, and pH.

(ii) Samples required:

(a) Triacetyloleandomycin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package or each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container in the samples submitted in accordance with subparagraph (3) (ii) (b) and (c) of this paragraph; $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (a) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148m.2 (b) (1) (ii) or (iii), except prepare the sample as follows: Reconstitute the drug as directed in the labeling. Transfer an appropriate sample (usually 1.0 milliliter) to a 100-milliliter volumetric flask and dilute to mark with 80 percent isopropyl alcohol-water solution. Further dilute an aliquot of this solution to the prescribed reference concentration in 0.2*M* potassium phosphate buffer, pH 10.5, if the plate assay is used, or in 1 percent potassium phosphate buffer, pH 6.0, if the turbidimetric assay is used. Its triacetyloleandomycin content is satisfactory if it contains not less than 90 percent nor more than 120 percent of the number of milligrams of triacetyloleandomycin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter, except use the suspension obtained after constituting the drug as directed in its labeling.

§ 148n.25 Oxytetracycline hydrochloride–hydrocortisone aerosol topical.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxytetracycline hydrochloride-hydrocortisone areosol topical is oxytetracycline hyrochloride and hydrocortisone in a suitable ointment base, packaged with one or more suitable inert gasgases. Each spray pack contains 300 milligrams of oxytetracycline and 100 milligrams of hydrocortisone. The moisture content is not more than 1.0 percent. The oxytetracycline hydrochloride used conforms to the standards prescribed by § 148n.2(a) (1) (i), (vi), (vii), (viii), and (ix). Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The oxytetracycline hydrochloride used in making the batch for potency, moisture, pH, absorptivity, identity, and crystallinity.

(b) The batch for potency and moisture.

(ii) Samples required:

(a) The oxytetracycline hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) (a), (b), and (c) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148n.1 (b) (1) (i) or (ii), except prepare the sample for assay as follows: Remove the cap and plastic spray tip from the aerosol can. Attach a 10-inch length of suitable plastic tubing over the nozzle of the aerosol can. Shake the can gently two or three times, place the free end of the tubing into a 400-milliliter beaker, hold the can in an upright position and depress the nozzle. Empty the entire contents into the beaker. Carefully evaporate any residual propellant by heating the beaker over a steam bath. Rinse the tubing with a minimum amount of ethyl alcohol and add it to the contents in the beaker. Transfer the contents of the beaker with three 10-milliliter portions of ethyl alcohol to a 1-liter volumetric flask. Bring to volume with 0.1*N* hydrochloric acid and mix well. Filter 40 to 50 milliliters of this stock solution through a double thickness of filter paper, discarding the first 20 milliliters of filtrate. Remove an appropriate aliquot of the remaining filtrate and, using 0.1*M* potassium phosphate buffer, pH 4.5, make proper estimated dilutions to the prescribed reference concentration. Its content of oxytetracycline is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141b.117(c) of this chapter.

§ 148n.26 Oxytetracycline hydrochloride-polymyxin B sulfate-hydrocortisone aerosol topical.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxytetracycline hydrochloride-polymyxin B sulfate-hydrocortisone aerosol topical is oxytetarcycline hydrochloride, polymyxin B sulfate, and hydrocortisone in a suitable ointment base, packaged with one or more suitable inert gases. Each spray pack contains 300 milligrams of oxytetracyline, 100,000 units of polymyxin B, and 100 milligrams of hydrocortisone. The moisture content is not more than 1.0 percent. The oxytetracyline hydrochloride used conforms to the standards prescribed by § 148n.2 (a) (1) (i), (vi), (vii), (viii), and (ix). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1 (a) (1) (i), (v), (vi), (vii), and (ix) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The oxytetracycline hydrochloride used in making the batch for potency, moisture, pH, absorptivity, crystallinity, and identity.

(b) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(c) The batch for oxytetracycline content, polymyxin content, and moisture.

(ii) Samples required:

(a) The oxytetracycline hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(b) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(c) The batch: A minimum of six immediate containers.

(d) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (c) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (a), (b), and (d) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Oxytetracycline content.* Proceed as directed in § 148n.25(b) (1) of this chapter. The content of oxytetracycline is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain.

(ii) *Polymyxin content.* Remove the cap and plastic spray tip from the aerosol can. Attach a 10-inch length of suitable plastic tubing over the nozzle and shake the can gently. Place the free end of the tubing into a beaker of suitable size, hold the can upright, and depress the nozzle until the contents are completely emptied into the beaker. Carefully evaporate any residual propellant by heating the beaker over a steam bath. Proceed as directed in § 148n.20(b) (1) (ii) (a) or (b), except in lieu of weighing 1 gram of the sample, use the entire contents obtained. The content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 135 percent of the number of units of polymyxin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141b.117(c) of this chapter.

§ 148n.27 Oxytetracycline hydrochloride-polymyxin B sulfate topical powder.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxytetracycline hydro-

chloride-polymyxin B sulfate topical powder is oxytetracycline hydrochloride and polymyxin B sulfate with a suitable filler. Each gram contains 30 milligrams of oxytetracycline and 10,000 units of polymyxin B. The moisture content is not more than 2.0 percent. The oxytetracycline hydrochloride used conforms to the standards prescribed by § 148n.2 (a) (1) (i), (vi), (vii), (viii), and (ix). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1 (a) (1) (i), (v), (vi), (vii), and (ix) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxytetracycline hydrochloride used in making the batch for potency, moisture, pH, absorptivity, crystallinity, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(*c*) The batch for oxytetracycline content, polymyxin content, and moisture.

(ii) Samples required:

(*a*) The oxytetracycline hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Oxytetracycline content.* Proceed as directed in § 148n.1(b) (1) (i) or (ii), except prepare the sample for assay as follows: Place an accurately weighed representative portion in a 1-liter volumetric flask, dissolve, and dilute to volume with 0.1*N* hydrochloric acid. Make the proper estimated dilutions of an aliquot of the stock solution to the prescribed reference concentration in 0.1*M* potassium phosphate buffer, pH 4.5. The content of oxytetracycline is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148p.1(b) (1) of this chapter, except prepare the sample for assay by either of the following methods:

(*a*) Accurately weigh approximately 1 gram of the powder and place in a 50-milliliter centrifuge tube. Add 15 milliliters of butyl alcohol and 1 drop of concentrated hydrochloric acid. Stir well. Add 20 milliliters of butyl alcohol and centrifuge for 10 minutes at 3,000 revolutions per minute. Decant the supernatant liquid and add 15 milliliters of acetone and 1 drop of concentrate hydrochloric acid to the residue. Stir well. Add 20 milliliters of acetone and centrifuge for 10 minutes at 3,000 revolutions per minute. Decant the supernatant liquid and repeat the acetone-acid extraction once more. Dissolve and dilute the residue with sufficient 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Remove an aliquot and make proper estimated dilutions to the prescribed reference concentration with 10 percent potassium phosphate buffer, pH 6.0.

(*b*) Place the accurately weighed sample in a filter funnel with a solvent-resistant membrane filter of 1.5μ porosity. Wash the powder with five 20-milliliter portions of acetone or until yellow color has disappeared. Remove the filter and soak in an adequate volume of 10 percent potassium phosphate buffer, pH 6.0. Quantitatively transfer to a 100-milliliter volumetric flask and adjust to volume with 10 percent potassium phosphate buffer, pH 6.0. Make proper estimated dilutions with 10 percent potassium phosphate buffer, pH 6.0, to the prescribed reference concentration.

The content of polymyxin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of polymyxin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148n.28 Oxytetracycline hydrochloride-polymyxin B sulfate-benzocaine for otic solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxytetracycline hydrochloride-polymyxin B sulfate-benzocaine for otic solution is a dry powder of oxytetracycline hydrochloride and polymyxin B sulfate, packaged in combination with a suitable diluting solution which contains benzocaine and a preservative. When prepared as directed in the labeling, each milliliter contains 5.0 milligrams of oxytetracycline, 10,000 units of polymyxin B, and 50 milligrams of benzocaine. The moisture content of the powder is not more than 3.0 percent. The oxytetracycline hydrochloride used conforms to the standards prescribed by § 148n.2(a) (1) (i), (vi), (vii), (viii), and (ix). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a) (1) (i), (v), (vi), (vii), and (ix) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of the chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxytetracycline hydrochloride used in making the batch for potency, moisture, pH, absorptivity, crystallinity, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(*c*) The batch for oxytetracycline content, polymyxin content, and moisture content of the powder.

(ii) Samples required:

(*a*) The oxytetracycline hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of seven immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3) (ii) (*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Oxytetracycline content.* Proceed as directed in § 148n.1(b) (1) (i) or (ii), except prepare the sample for assay as follows: Reconstitute as directed in the labeling. Dilute 5.0 milliliters of this reconstituted sample to a volume of 100 milliliters with 0.1*N* hydrochloric acid. Make proper estimated dilutions to the prescribed reference concentration with 0.1*M* potassium phosphate buffer, pH 4.5. The content of oxytetracycline is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148n.27(b) (1) (ii) (*a*) or (*b*), except use the entire contents of the powder from each vial tested. Reconstitute a separate vial as directed in the labeling, measure the total volume that can be withdrawn, and, from the polymyxin content of the powder, calculate the number of units per milliliter. The content of polymyxin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of units of polymyxin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148n.29 Oxytetracycline hydrochloride-polymyxin B sulfate vaginal tablets.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Oxytetracycline hydrochloride-polymyxin B sulfate vaginal tablets are tablets composed of oxytetracycline hydrochloride and polymyxin B sulfate, with one or more suitable diluents, binders, lubricants, and preservatives. Each tablet contains 100 milligrams of oxytetracycline and 100,000 units of polymyxin B. The moisture content is not more than 3.0 percent. The oxytetracycline hydrochloride used conforms to the standards prescribed by § 148n.2(a)(1) (i), (vi), (vii), (viii), and (ix). The polymyxin B sulfate used conforms to the standards prescribed by § 148p.1(a)(1) (i), (v), (vi), (vii), and (ix) of this chapter. Each other ingredient used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with the requirements of § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The oxytetracycline hydrochloride used in making the batch for potency, moisture, pH, absorptivity, crystallinity, and identity.

(*b*) The polymyxin B sulfate used in making the batch for potency, moisture, pH, residue on ignition, and identity.

(*c*) The batch for oxytetracycline content, polymyxin content, and moisture.

(ii) Samples required:

(*a*) The oxytetracycline hydrochloride used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*c*) The batch: A minimum of 30 tablets.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $1.00 for each tablet in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Oxytetracycline content.* Proceed as directed in § 148n.1(b)(1) (i) or (ii), except prepare the sample as follows: Place a representative number of tablets in a glass blending jar and blend 3 to 5 minutes with an appropriate volume of 0.1*N* hydrochloric acid to give a stock solution of convenient concentration. Its content of oxytetracycline is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of milligrams of oxytetracycline that it is represented to contain.

(ii) *Polymyxin content.* Proceed as directed in § 148n.27(b)(1)(ii) (*a*) or (*b*), using the finely powdered material from a representative number of tablets. Its content of polymyxin is satisfactory if it contains not less than 90 percent and not more than 120 percent of the number of units of polymyxin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148p.7 Polymyxin B sulfate-gramicidin-hydroxyamphetamine hydrobromide-methapyrilene hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Polymyxin B sulfate-gramicidin-hydroxyamphetamine hydrobromide-methapyrilene hydrochloride nasal solution is a solution containing, in each milliliter, 500 units of polymyxin B, 0.05 milligram of gramicidin, 10.0 milligrams of hydroxyamphetamine hydrobromide, and 2.0 milligrams of methapyrilene hydrochloride. It contains one or more suitable solvents, surfactants, buffers, colorings, and preservatives. Its pH is not less than 5.0 and not more than 6.0. The polymyxin B sulfate used conforms to the standards of § 148p.1(a)(1) (i), (iv), (vi), (vii), and (ix). The gramicidin used conforms to the standards of § 148f.1(a)(1) (i), (ii), (iv), (v), and (vi) of this chapter. Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The polymyxin B sulfate used in making the batch for potency, toxicity, pH, residue on ignition, and identity.

(*b*) The gramicidin used in making the batch for potency, toxicity, residue on ignition, melting point, identity, and crystallinity.

(*c*) The batch for: Polymyxin content, gramicidin content, and pH.

(ii) Samples required:

(*a*) The polymyxin B sulfate used in making the batch: 10 packages, each containing approximately 300 milligrams.

(*b*) The gramicidin used in making the batch: 10 packages, each containing approximately 500 milligrams.

(*c*) The batch: A minimum of six immediate containers.

(*d*) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $5.00 for each immediate container in the sample submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph; $4.00 for each package submitted in accordance with subparagraph (3)(ii) (*a*), (*b*), and (*d*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency*—(i) *Polymyxin content.* Remove an accurately measured representative portion and dilute with 10 percent potassium phosphate buffer, pH 6.0, to give a stock solution of convenient concentration. Further dilute with 10 percent potassium phosphate buffer, pH 6.0, to a reference concentration of 10 units of polymyxin per milliliter. Proceed as directed in § 148p.1(b)(1), except add 300 milligrams of thioglycolic acid to each liter of agar used for the seed layer. The polymyxin content is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of units of polymyxin that it is represented to contain.

(ii) *Gramicidin content.* Proceed as directed in § 148f.1(b)(1) of this chapter, except prepare the sample for assay as follows: Remove an accurately measured representative portion and dilute with 95 percent alcohol to give a stock solution of convenient concentration. Further dilute with 95 percent alcohol to the prescribed reference concentration. The content of gramicidin is satisfactory if it is not less than 90 percent and not more than 125 percent of the number of milligrams of gramicidin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted sample.

§ 148r.2 Tyrothricin solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin solution is tyrothricin and a suitable preservative dissolved in a vehicle of alcohol and propylene glycol. Each milliliter contains 25 milligrams of tyrothricin. The pH of a solution prepared by mixing 1 milliliter of the concentrate with 49 milliliters of distilled water is not less than 5.0 and not more than 6.5. The tyrothricin used conforms to the standards prescribed by § 148r.1(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The tyrothricin used in making the batch for potency, moisture, and identity.

(*b*) The batch for potency and pH.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 1 gram.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.1 (b) (1), except prepare the sample for assay as follows: Transfer the contents of a vial to a 1,000-milliliter volumetric flask, adjust to volume with distilled water, and mix well. Make proper estimated dilutions of an aliquot to the reference concentration with 95 percent alcohol. Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, except use a solution prepared by mixing 1 milliliter of the concentrate with 49 milliliters of distilled water.

§ 148r.3 Tyrothricin-antipyrine-benzocaine-hexylresorcinol otic solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin-antipyrine-benzocaine-hexylresorcinol otic solution is tyrothricin, antipyrine, benzocaine, and hexylresorcinol dissolved in a vehicle of propylene glycol and glycerin. Each milliliter contains 0.5 milligrams of tyrothricin, 50 milligrams of antipyrine, 12.5 milligrams of benzocaine, and 1.0 milligram of hexylresorcinol. The moisture content is not more than 2.0 percent. The pH is not less than 5.5 and not more than 7.5. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency, moisture, and pH.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.1 (b) (1), except prepare the sample for assay as follows: Remove an accurately measured representative portion with a suitable syringe and appropriately dilute with 95 percent alcohol to yield a stock solution of convenient concentration. Make proper estimated dilutions with 95 percent alcohol to the prescribed reference concentration. Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.8(b) of this chapter.

(3) *pH.* Proceed as directed in § 141a.5(b) of this chapter using the undiluted sample.

§ 148r.4 Tyrothricin cream.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin cream is tyrothricin, with or without one or more suitable solvents, surfactants, and preservatives, in a suitable cream base. Each gram contains 0.5 milligram of tyrothricin. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(a) The batch mark.

(b) The name and quantity of each active ingredient contained in the drug.

(c) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay; potency.* Proceed as directed in § 148r.1 (b) (1), except prepare the sample for assay as follows: Transfer an accurately weighed representative portion to a separatory funnel and add 25 milliliters of petroleum ether. Shake the contents until the cream is dispersed. Add 50 milliliters of 80 percent ethyl alcohol and shake well. Allow the phases to separate. Transfer the alcohol phase to a second separatory funnel. Add 25 milliliters of petroleum ether, shake for 2 or 3 minutes and allow the phases to separate. Repeat the extraction again if necessary. Collect the alcohol layer in a 100-milliliter volumetric flask, adjust to mark with 80 percent alcohol, and shake well. Make proper estimated dilutions to the reference concentration with 95 percent alcohol. Its content of tyrothricin is satisfacotry if it is not less than 90 percent and not more than 140 percent of the number of milligrams of tyrothricin that it is represented to contain.

§ 148r.5 Tyrothricin-methapyrilene hydrochloride-benzocaine cream.

Tyrothricin-methapyrilene hydrochloride-benzocaine cream conforms to all requirements and is subject to all procedures prescribed by § 148r.4 for tyrothricin cream, except that each gram of cream contains 0.25 milligram of tyrothricin, 20 milligrams of methapyrilene hydrochloride, and 20 milligrams of benzocaine.

§ 148r.6 Tyrothricin-phenylpropanolamine hydrochloride nasal solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin-phenylpropanolamine hydrochloride nasal solution is tyrothricin and phenylpropanolamine hydrochloride dissolved in an aqueous vehicle, with one or more suitable solvents, buffer substances, and colorings. Each milliliter contains 0.2 milligram of tyrothricin and 15 milligrams of phenylpropanolamine hydrochloride. Its pH is not less than 5.5 and not more than 6.5. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(a) The batch mark.

(b) The name and quantity of each active ingredient contained in the drug.

(c) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency and pH.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.3 (b) (1). Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 120 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter.

§ 148r.7 Tyrothricin - pantothenyl alcohol mouthwash.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin-pantothenyl alcohol mouthwash is tyrothricin and pantothenyl alcohol with one or more suitable solvents, surfactants, colorings, and flavorings in an aqueous vehicle. Each milliliter contains 0.2 milligram of tyrothricin and 0.2 milligram of pantothenyl alcohol. Its pH is not less than 5.0 and not more than 7.0. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(a) The batch mark.

(b) The name and quantity of each active ingredient contained in the drug.

(c) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency and pH.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.3-(b) (1). Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, except use the undiluted solution.

§ 148r.8 Tyrothricin-benzocaine troches; tyrothricin-propyl *p*-aminobenzoate troches.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Each tyrothricin-benzocaine troche contains 1.0 milligram of tyrothricin and 5.0 milligrams of benzocaine, with or without one or more suitable fillers, binders, lubricants, colorings, and flavorings. Each tyrothricin-propyl *p*-aminobenzoate troche contains 2.0 milligrams of tyrothricin and 2.0 milligrams of propyl *p*-aminobenzoate, with or without one or more suitable and harmless fillers, binders, lubricants, colorings, and flavorings. The moisture content is not more than 1.5 percent. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(a) The batch mark.

(b) The name and quantity of each active ingredient contained in the drug.

(c) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use of the drug.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency and moisture.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of 30 troches.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $0.75 for each troche submitted in accordance with subparagraph (3) (ii) (b) of this paragraph; $4.00 for each package in the samples submitted in accordance with subparagraph (3) (ii) (a) and (c) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.1(b) (1), except prepare the sample for assay as follows: Place a representative number of troches into a flask of suitable size. Add a quantity of 95 percent ethyl alcohol that will give a stock solution of convenient concentration. Stopper the flask and place on a mechanical shaker. Allow to shake until the troches are dissolved. Make proper estimated dilutions with 95 percent alcohol to the reference concentration. Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 140 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *Moisture.* Proceed as directed in § 141a.5(a) of this chapter.

§ 148r.9 Tyrothricin - triethanolamine polypeptide cocoate condensate solution.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality and purity.* Tyrothricin-triethanolamine polypeptide cocoate condensate solution contains, per milliliter, 1.0 milligram of tyrothricin and 120 milligrams of triethanolamine polypeptide cocoate, with one or more suitable solubilizing agents, perfumes, buffer substances, and preservatives, in distilled water. Its pH is not less than 5.5 and not more than 6.5. The tyrothricin used conforms to the standards prescribed by § 148r.1(a) (1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed therefor by such official compendium.

(2) *Labeling.* It shall be labeled in accordance with § 148.3 of this chapter. Its expiration date is 12 months.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(a) The tyrothricin used in making the batch for potency, moisture, and identity.

(b) The batch for potency and pH.

(ii) Samples required:

(a) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(b) The batch: A minimum of five immediate containers.

(c) In case of an initial request for certification, each other ingredient used in making the batch: One package of each containing approximately 5 grams.

(4) *Fees.* $4.00 for each immediate container or package in the samples submitted in accordance with subparagraph (3) (ii) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.3 (b) (1). Its content of tyrothricin is satisfactory if it is not less than 90 percent and not more than 130 percent of the number of milligrams of tyrothricin that it is represented to contain.

(2) *pH.* Proceed as directed in § 141a.5(b) of this chapter, using the undiluted solution.

§ 148r.10 Tyrothricin-nitrofurazone adhesive bandage.

(a) *Requirements for certification*—(1) *Standards of identity, strength, quality, and purity.* Tyrothricin-nitrofurazone adhesive bandage is a gauze or flannel compress impregnated with tyrothricin and nitrofurazone, covered with a transparent porous material, and affixed to a perforated pliable plastic strip which is coated on one surface with a pressure-sensitive adhesive. The folded gauze compress has dimensions of ⅞ by 1 inch, ⅝ by 1 inch, 23/32 by 9/16 inch, or 9/32 by ½ inch. The flannel compress is round with a diameter of 10 millimeters. The bandage is enclosed in a sealed paper wrapper. Each gram of gauze or flannel compress contains not less than 0.1 milligram each of tyrothricin and nitrofurazone. It is sterile. The tyrothricin used conforms to the standards prescribed by § 148r.1(a)(1). Each other substance used, if its name is recognized in the U.S.P. or N.F., conforms to the standards prescribed by such official compendium.

(2) *Labeling.* Each package shall bear on its label or labeling, as hereinafter indicated, the following:

(i) On the label of the immediate container and on the outside wrapper or container, if any:

(*a*) The batch mark.

(*b*) The name and quantity of each active ingredient contained in the drug.

(*c*) An expiration date that is 12 months after the month during which the batch was certified.

(ii) On the label of the immediate container or other labeling attached to or within the package, adequate directions for lay use.

(3) *Requests for certification; samples.* In addition to the requirements of § 148.4 of this chapter, each such request shall contain:

(i) Results of tests and assays on:

(*a*) The tyrothricin used in making the batch for potency, moisture, and identity.

(*b*) The impregnated gauze or flannel used in making the batch for potency.

(*c*) The batch for potency and sterility.

(ii) Samples required:

(*a*) The tyrothricin used in making the batch: Five packages, each containing approximately 300 milligrams.

(*b*) The impregnated gauze or flannel used in making the batch: Five pieces, each approximately 1 square yard in area.

(*c*) The batch:

(*1*) For potency testing: 30 bandages each of the gauze type and of the flannel type.

(2) For sterility testing: 10 bandages of the ¾- by 3-inch size from each sterilizer load or, if such size is not included, 10 bandages of the largest size bandage from each sterilizer load.

(4) *Fees.* $4.00 for each sample submitted in accordance with subparagraph (3)(ii)(*a*) of this paragraph; $6.00 for each sample submitted in accordance with subparagraph (3)(ii)(*b*) of this paragraph; $1.00 for each bandage submitted in accordance with subparagraph (3)(ii)(*c*) of this paragraph.

(b) *Tests and methods of assay*—(1) *Potency.* Proceed as directed in § 148r.1(b)(1), except prepare the sample for assay as follows: Dip a representative number of bandages in a mixture containing equal parts of petroleum ether and carbon tetrachloride in order to remove the compresses. Allow the compresses to air dry for 5 minutes. Accurately weigh 0.4 gram of gauze, or 0.1 gram if the compress is composed of flannel. If the sample is the impregnated gauze or flannel used in making the bandages, cut out approximately 12 square inches of the material and weigh it accurately. Place the weighed sample in a glass-stoppered flask and add sufficient 95 percent ethyl alcohol to give a stock solution of convenient concentration. Stopper the flask and place it in a 37° C. incubator for ½ hour. Further dilute the stock solution with sufficient 95 percent ethyl alcohol to obtain the prescribed reference concentration of tyrothricin. Its content of tyrothricin is satisfactory if it is not less than 0.1 milligram per gram of material.

(2) *Sterility.* Use 10 bandages of the ¾- by 3-inch size and proceed as directed in § 141.2(e)(2) of this chapter except aseptically remove the paper wrapper and lift, but do not remove, both sections of the protective, translucent plastic strips until the compress is exposed. Place one such bandage into each of five tubes of medium A and one into each of five tubes of medium E.

Dated: October 9, 1964.

GEO. P. LARRICK,
Commissioner of Food and Drugs.

[F.R. Doc. 64-10545; Filed, Oct. 16, 1964; 8:45 a.m.]

UNIVERSITY OF MICHIGAN
OCT 30 1964
READING ROOM

Pages 14397–14428

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VOLUME 29 NUMBER 205

Washington, Tuesday, October 20, 1964

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